Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

30-Mar-99

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Subject: Response to Draft Guidance for Industry: BACPAC I: Intermediates in Drug Substance Synthesis, (Federal Register, 30-Nov-98, Docket 98D-0994)

To Whom It May Concern:

Novartis Pharmaceuticals Corporation ("Novartis") has reviewed the above-referenced draft guidance. Specific comments, identified by line number, are provided in tabular form in the enclosure.

Overall, Novartis believes that this guidance will provide significant regulatory relief. However, in order to achieve regulatory relief, the scope of the guidance document needs to be clarified to refer only to changes to what has already been filed to a NDA, not *all* changes, as is implied throughout the draft document.

The requirement of test documentation is generally fair and scientifically driven. However, the requirement to submit documentation that is not typically provided in a NDA (analytical methods of early intermediates, validation data for intermediates, detailed lists of equipment, manufacturing scale changes, vendors for starting materials) will discourage changes that would provide increased efficiencies, consistency, etc. Also, the definition of historical data as that generated from ten premodification batches may be statistically significant, but is not practical. The guidance does not present alternative requirements in the likely event that ten batches are not available, other than contacting the reviewing division.

Thank you for the opportunity to comment. If you have any questions, please contact Dr. Mathias Hukkelhoven at (973) 781-6035 or Donna Kapples at (973) 781-6929.

Sincerely,

Thomas Koestler, PhD
Vice President, Head
Drug Regulatory Affairs

Enclosures: Comments provided in duplicate

98D-0994 C23

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Novartis' Comments on the Draft BACPAC I Guidance

Line	Comments
73	The guidance does not allow industry to report even minor updates/changes via the DMF Annual Report. The rules should be the same regardless of NDA or DMF.
120	Validation data of new methods of manufacturing early intermediates should not be a requirement for submission. Recommend changing "validation data should be provided" to "the methods should be appropriately validated" throughout the entire guidance document.
124	Historical data on ten premodification batches may be statistically significant, but not practical. Novartis recommends inclusion of pilot scale or validation batches in the "10".
165	Clarification required: When a material is outsourced, "adequate release or acceptance testing, as appropriate" should be carried out. Does this need to be included in the submission?
167	Site changes should also be allowed based on data from pilot scale batches.
173	Additional purification procedures (or repetition of an existing procedure on a routine basis) to achieve equivalence with prechange material **on** the final intermediate should be covered under BACPAC II if it is not the scope of BACPAC I.
196	Clarification required: Can pilot scale drug substance be used as the postmodification batches to demonstrate physical property equivalence?
220	The new site, which may be within a single facility, within a contiguous campus, or in a different campus, should have similar **or better** environmental controls.
241	Clarification required: Analytical methods of early intermediates are not typically submitted to a NDA. Novartis proposes that it would be sufficient to submit the type of methodology employed.
259	A certificate of analysis from the manufacturer for each outsourced intermediate affected by a site change is not value added.

273	Scale Changes - propose deleting the entire section. A scale change would more than likely be a result of other changes.
275	No attempt is made to classify scale changes according to the magnitude of the change. This is inconsistent with current industry practice where a scale factor increase/decrease of 10 has been implemented without notification.
314	Equipment information is not typically filed to a NDA. This section should apply only to equipment changes made to "previously filed" equipment.
319	Change "previously used" to "previously filed".
328	If analytical method changes for the final intermediate are covered under BACPAC I, then specification changes to the final intermediate should also be included in BACPAC I. Often, a change to the method may result in a specification change, therefore it would be more practical to keep these together in the same guidance.
395	The reporting requirement for a specification change for a solvent or reagent should be the annual report, without the prerequisite to contact the division. Novartis finds it reasonable to report a specification change to a starting material in a Changes Being Effected supplement.
442	The reporting requirement for a manufacturing process change that does not involve new starting materials or intermediates should be the annual report if equivalency of the impurity profiles is demonstrated at or before the final intermediate.
501	A list of sources (including commercial vendors and contract manufacturers) should not be a requirement for submission, but instead be available for inspection. Changes in starting material sources should not require FDA action, as long as new sources meet established specifications and impurity profiles at the next appropriate step.
503	A change control protocol (to establish the suitability of a new supplier or when an existing supplier's process is changed) is not normally submitted to a NDA because it is considered GMP. But if a change protocol is submitted, then this would imply that a once the protocol is approved, then the company should be allowed to make changes according to the approved protocol via the annual report.
624	Polymorphism is not part of the scope of ICH Q3A, Impurities in New Drug Substances.

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NOVARTIS PHARMACEUTICAL CORPOR 1 LBS
(973)781-5495
INTERNAL DISTRIBUTION
101 - MAILROOM - 033199
59 STATE HWY 10
EAST HANOVER NJ 07936-1946

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